PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 02 September 1998 (02.09.98)	
International application No. PCT/GB98/00095	**Applicant's or agent's file reference** SMW/BP5674577
International filing date (day/month/year) 13 January 1998 (13.01.98)	**Priority date** (day/month/year) 13 January 1997 (13.01.97)
Applicant JACKSON, Stephen, Philip et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

12 August 1998 (12.08.98)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer C. Cupello
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
SMW/BP5674577		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 98/00095	13/01/1998	13/01/1997

Applicant

CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED et al.

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] **Certain claims were found unsearchable** (see Box I).

2. [ ] ***Unity of invention is lacking*** (see Box II).

3. [X] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the *international search was carried out on the basis of the sequence listing*

   [ ] filed with the international application.

   [X] furnished by the applicant separately from the international application,

   [ ] *but not accompanied by a statement to the effect that it did not include* matter going beyond the disclosure in the international application as filed.

   [ ] Transcribed by this Authority

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. *With regard to the* **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. 5

   [X] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 98/00095

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: -
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Although claims 20, 23 and 26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the modulating compound.

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Interna[redacted]l Application No
PC[redacted] 98/00095

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 G01N33/50 G01N33/68 C12N9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 17189 A (SALK INST FOR BIOLOGICAL STUDI) 4 August 1994 see claims 19-22 ---	1-28
X	POLTORATSKY, V.P. ET AL.: "human DNA activated protein kinase (DNA-PK) is homologous to phosphatidylinositol kinase." THE JOURNAL OF IMMUNOLOGY, 1995, pages 4529-44533, XP002065031 see the whole document --- -/--	7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 May 1998	19. 06. 1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hoekstra, S

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HIDAKA, H. ET AL.: "Methods in Enzymology volume 201; Protein phosphorylation part B analysis of protein phophorylation, protein kinas inhibitors and protein phosphatases; Ed. T. Hunter and B.M. Sefton; Chapter 27: "Properties and use of H-series compounds as protein kinase inhibitors" 1991 , ACADEMIC PRESS , SAN DIEGO XP002065037 see page 328 - page 339 ---	7
X	WEI, Y-F, ET AL.: "Molecular cloning and expression of human cDNAs encoding a novel DNA ligase IV and DNA ligase III, an enzyme active in DNA repair and recombination" MOLECULAR AND CLELLULAR BIOLOGY, vol. 15, no. 6, June 1995, pages 3206-3216, XP002065032 see the whole document ---	12
Y	GAKEN, JOOP A. ET AL: "Efficient retroviral infection of mammalian cells is blocked by inhibition of poly(ADP-ribose) polymerase activity" J. VIROL. (1996), 70(6), 3992-4000 CODEN: JOVIAM;ISSN: 0022-538X, XP002061469 see the whole document ---	1-28
Y	KACZMARSKI, WOJCIECH ET AL: "Lupus autoantigen Ku protein binds HIV-1 TAR RNA in vitro" BIOCHEM. BIOPHYS. RES. COMMUN. (1993), 196(2), 935-42 CODEN: BBRCA9;ISSN: 0006-291X, XP002061470 see the whole document ---	1-28
P,X	GRAWUNDER, U. ET AL.: "Activity of DNA ligase IV stimulated by complex formation with XRCC4 protein in mammalian cells" NATURE, vol. 388, 31 July 1997, pages 492-495, XP002065033 see the whole document ---	1-28
P,X	CRITCHLOW, S. E. ET AL.: "Mammalian double strand break repair protein XRCC4 interacts with DNA ligase IV." CURRENT BIOLOGY, vol. 7, no. 8, 1 August 1997, page 588-598 XP002065034 see the whole document --- -/--	1-28

1

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	TOMKINSON, A.E. ET AL.: "structure and function of mammalian DNA ligases" MUTAT. RES., vol. 407, no. 1, January 1998, pages 1-9, XP002065035 see the whole document	8-10
A	WO 96 30524 A (HUMAN GENOME SCIENCES INC ;WEI YING FEI (US); YU GUO LIANG (US); H) 3 October 1996	1-28
A	WO 95 10288 A (BAYLOR COLLEGE MEDICINE) 20 April 1995 see claim 1	1-28
A	SALLES B ET AL: "RAPID QUANTIFICATION OF DNA REPAIR SYNTHESIS IN CELL EXTRACTS" ANALYTICAL BIOCHEMISTRY, vol. 215, 1993, pages 304-306, XP002054958 see the whole document	1-28
A	HARTLEY, K. ET AL.: "DNA-dependent protein kinase catalytic subunit: A relative of phosphatidylinositol 3-kinase and the Ataxia telangiectasia gene product" CELL, vol. 82, 8 September 1995, pages 849-856, XP002065036 see abstract; figures 1-28	1-28

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna[redacted]l Application No
PC[redacted] 98/00095

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9417189 A	04-08-1994	CA 2132452 A	04-08-1994
		EP 0632832 A	11-01-1995
		JP 7505057 T	08-06-1995
		US 5627064 A	06-05-1997
		US 5686412 A	11-11-1997
WO 9630524 A	03-10-1996	AU 2201695 A	16-10-1996
WO 9510288 A	20-04-1995	AU 7972594 A	04-05-1995

File copy

PCT/GB98/00095

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PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

WALTON, Seán, M.
Mewburn Ellis
York House
23 Kingsway
London WC2B 6HP
ROYAUME-UNI

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year)
08 July 1999 (08.07.99)

Applicant's or agent's file reference
SMW/BP5674677

IMPORTANT NOTIFICATION

International application No.
PCT/GB98/00095

International filing date (day/month/year)
13 January 1998 (13.01.98)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED
Cambridge House
6-10 Cambridge Terrace
Regent's Park
London NW1 4JL
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
KUDOS PHARMACEUTICALS LIMITED
327-329 Cambridge Science Park
Cambridge CB4 4GW
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
S. Cruz

Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

002721034

PATENT COOPERATION TREATY

REC'D 27 APR 1999
WIPO PCT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SMW/BP5674577		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB98/00095	13/01/1998	13/01/1997
International Patent Classification (IPC) or national classification and IPC G01N33/50		
Applicant CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ *This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have* been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12/08/1998	22. 04. 99
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Wallinder, E Telephone No. (+49-89) 2399 8435

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB98/00095

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-95	as originally filed				

Claims, No.:

1-8,9 (part),18 (part), 19-28	as originally filed				
9 (part),10-17, 18 (part)	as received on	28/01/1999	with letter of	27/01/1999	

Drawings, sheets:

1/11-11/11	as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-6, 9-11, 13, 14, 18-28
	No:	Claims	7, 8, 12, 15 to 17
Inventive step (IS)	Yes:	Claims	1-6, 9-11, 13, 14, 19-28
	No:	Claims	7, 8, 12, 15 to 18
Industrial applicability (IA)	Yes:	Claims	1-16, 19, 21, 22, 24, 25, 27, 28
	No:	Claims	17, 18, 20, 23 and 26 ??

2. Citations and explanations

see separate sheet

VI. *Certain documents cited*

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. *Certain observations on the international application*

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Ad Section I.

1). Sequence listing has been submitted on separate pages numbered 1 to 23.

Ad Section V.

2). Reference is made to the following documents:

D1 = WO-A-9 417 189

D2 = THE JOURNAL OF IMMUNOLOGY, 1995, Vol. 155, pages 4529-4533; POLTORATSKY, V. P. ET AL.: "Human DNA-Activated Protein Kinase (DNA-PK) is Homologous to Phosphatidylinositol Kinases".

D3 = HIDAKA, H. ET AL.: "Methods in Enzymology", Volume 201; Protein phosphorylation part B analysis of protein phosphorylation, protein kinas inhibitors and protein phosphatases; Ed. T. Hunter and B.M- Sefton; Chapter 27: "Properties and use of H-series compounds as protein kinase inhibitors". 1991, ACADEMIC PRESS; pages 328-339.

D4 = MOLECULAR AND CELLULAR BIOLOGY, Vol. 15, No. 6, June 1995, pages 3206-3216
WEI, Y-F, ET AL.: "Molecular cloning and expression of human cDNAs encoding a novel DNA ligase IV and DNA ligase III, an enzyme active in DNA repair and recombination".

D5 = CELL, Vol 83, 1995, pages 1079-1089
LI, Z. ET AL.: "The XRCC4 gene encodes a novel protein involved in DNA double-strand break repair and V(D)J recombination".

D6 = J. VIROL. (1996), Vol. 70, No.6 , pages 3992-4000;
GAKEN, J. A ET AL.: "Efficient retroviral infection of mammalian cells is blocked by inhibition of poly(ADP-ribose) polymerase activity".

D7 = BIOCHEM. BIOPHYS. RES. COMMUN. (1993), 196(2), PAGES 935-942;

KACZMARSKY, W. ET AL.: "Lupus autoantigen Ku protein binds HIV-1 TAR RNA *in vitro*".

The document D5 were not cited in the international search report. A copy of the document is appended hereto.

3). D1 relates to casein kinase which is a member of the HRR25-like kinases. These kinases function in a separate DNA repair pathway, distinct from the Ku-associated DNA repair pathway with which the present application is concerned, including the interaction with the XRCC4 protein.

D2 describes the cDNA sequence of DNA-activated protein kinase (DNA-PK). This kinase interacts with DNA end binding heterodimeric protein, Ku, and is activated by double-stranded DNA.

D3 is concerned with inhibitors of a variety of protein kinases, including A-kinase, G-kinase, C-kinase, MLCK etc.

D4 is acknowledged in the present application for example on page 5, line 8 and page 14, lines 7-8. This document identified the human DNA ligase IV cDNA sequence. D4 also refers to the purified DNA ligase IV obtained from human cells. Fragments of DNA ligase IV are also referred to in TABLE 1 on page 3210. However, the physiological role of DNA ligase IV, in particular that fragments of DNA ligase IV by the modulating interaction between the components identified by the present application is not referred to.

D5 refers to the identification of the XRCC4 gene. This gene encodes a small 334 amino acid residue protein of a calculated molecular weight of 38 kDa.

D6 is concerned with the nuclear enzyme poly (ADT-ribose) polymerase (PARP) which again functions in a separate DNA repair pathway from the Ku-associated DNA repair pathway. This has been demonstrated by a number of observations;

1. Disruptions of PARP and Ku pathways by surface inhibitors are distinct. In cells of animals which are genetically engineered to contain in the PARP pathway, the Ku pathway, or in both pathways, the result of defects in both

pathways together is far greater than in either pathway alone, indicating that defects are occurring in a combination of separate DNA repair pathways.

2. yeast cells contain no PARP but do have fully functional Ku homologues.

D7 demonstrates that Ku binds to HIV1 TAR RNA. However, This does not indicate any functional relevance. Indeed Ku binds to numerous RNA molecules, indicating that the binding to HIV TAR is not specific. The document is not concerned at all with interaction between DNA-PKcs/Ku and XRCC4 and/or DNA ligase IV. This document provides no teaching of the physiological relevance of these components.

4). The present invention in various aspects provides for modulating, interfering with or interrupting interaction between the XRCC4 protein and DNA ligase IV, using an appropriate agent. The present invention also provides in analogous aspects for modulating, interfering with or interrupting interaction between the XRCC4 protein and DNA-Pkcs/Ku, using an appropriate agent. One alternative is to screen for a compound that is able to affect DNA ligase IV activity.
D5 is the only paper published on the XRCC4 protein as such prior to the priority date of the present invention. It reports that XRCC4 is not related to any other proteins and so its sequence gives no clear clues as to its function. Therefore, the only assays available for XRCC4 were cellular radiosensitivity and cellular V(D)J recombination - assays that cannot be used as primary screens for inhibitors.
D4 referring to the identification of human DNA ligase IV cDNA sequence, does not disclose or make obvious the presently claimed methods.

5). It can be concluded that the assay methods according to Claims 1 and 2, as well as the methods according to Claims 3 to 6 and 19 to 28 (if Claims 19 to 27 are accordingly clarified, see point 11 beneath) are neither disclosed nor suggested by the cited prior art according to D1 to D7.
Therefore the subject-matter of Claims 1 to 6 and 19 to 28 is novel and based upon an inventive step.
The subject-matter of Claims 1 to 6 and 19 to 28, therefore, would appear to meet the requirements of Articles 33(2) and 33(3) PCT.

6). It would appear that D4 discloses purified DNA ligase IV as well as peptide fragments thereof and the cDNA encoding this enzyme (see abstract, TABLE 1 and 3211).
It would namely appear that agent according to Claim 7, 15 and 16 the peptide fragment of DNA ligase IV according to Claim 8 are disclosed in Thus, it would appear that at least some of the peptide fragments as referred to in TABLE 1 are closely related to the specific fragments as featured in Claims 9 to 11 and would therefore have the same effect as these peptide fragments. .
Thereby, as the peptide fragment according to Claim 8 is known from D1, the nucleic acid isolate according to Claim 12, encoding such a peptide, is also implicitly disclosed in D4.
In addition it would appear that the DNA-PK as disclosed in D2 and interacts with the DNA end binding heterodimeric protein Ku is an agent falling under the scope of Claims 7 and 16.
Additionally, from the last paragraph, right hand column, page 4532 in D2 it can be concluded that the use of DNA-PK in medicaments for modulating cellular DNA repair activity would appear to be obvious. The subject-matter of claims 17 and 18 is therefore obvious in view of D2
Furthermore, reference is made to D3 which discloses various protein kinase inhibitors. It would appear that the inhibitors as disclosed here would fall under the agent as claimed in Claims 7, 15, 16 and the first medical use as featured in Claim 17.

To sum up, Claims 7, 8, 12, 15 to 17 would appear to lack novelty and inventive step in view of D2, D3 or D4.
Furthermore, the subject-matter of Claim 18 would appear to be novel. However, it is lacking an inventive step in view of D2 or D5.
Therefore, the subject-matter of Claims 7, 8, 12, 15 to 17 does not meet the requirements of Article 33(2) PCT.
The subject-matter of Claims 7, 8, 12, 15 to 18 does not meet the requirements of article 33(3) PCT.

The specific peptides as featured in Claims 9 to 11 would appear to be novel and inventive. They are not disclosed or suggested in any of the citations according to D1 to D7.

Therefore, the subject-matter of Claims 9 to 11 would appear to meet the requirements of Articles 33(2) and 33(3) PCT.
Reference is made to D5 disclosing the XRCC4 protein and the nucleic acid encoding this fragment. However, claim 13 featuring a peptide fragment of XRCC4 capable of modulating interaction between XRCC4 and DNA ligase IV would appear to be novel over D5. XRCC4 is a protein of 334 amino acids and therefore not considered as a peptide fragment. That XRCC4 and DNA ligase IV interact is a novel and inventive feature of the present invention, not known or suggested in the prior art. The subject-matter of Claims 13 as well as that of Claim 14 is therefore considered as novel and inventive.
Therefore the subject-matter of Claims 13 and 14 would appear to meet the requirements of Articles 33(2) and 33(3) PCT.

7). It would appear that the subject-matter of Claims 1 to 16 and 19, 21, 22, 24, 25 and 27 to 28 is industrially applicable.
The subject-matter of these Claims would therefore appear to meet the requirements of Article 33(4) PCT.

For the assessment of the present claims 17, 18, 20, 23 and 26 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The EPO would therefore acknowledge as industrially applicable the subject-matter of Claims 17 and 18.

Ad Section VI.

8). The current assessment is based on the assumptions that all Claims enjoy priority rights from the filing date of the priority documents. If it later turns out that this is correct, the documents cited in the search report, namely GRAWUNDER, U. ET AL.: NATURE, Vol. 388, 31 July 1997, pages 492-495; CRITCHLOW, S. E. ET

AL.: CURRENT BIOLOGY, Vol 7, No. 8, 1 August 1997, page 588-598; and TOMKINSON, A. E. ET AL.: in MUTAT. RES. Vol 407, No. 1, January 1998, pages 1- 9, could become relevant.

Ad Section VII.

9). Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1, D3, D6 and D7 are not mentioned in the description, nor are these documents identified therein.

Ad Section VIII.

10). It would appear that the broad term "agent" as defined in Claims 7, 15 to 18 lacks clarity with regard to its scope. The term "agent" can therefore not be accepted under Article 6 PCT.
Thus, a definition, which only relates to the ability of modulating interaction between XRCC4 and DNA ligase IV and/or DNA-PKCS/Ku as featured in the Claims, is not sufficient to restrict and limit the agent to novel substances.

11). Furthermore, in method Claims 19 to 27 referring to "A method which includes,..." it should be made clear that also the methods referred to in this Claims, namely method according to Claim 1 or Claim 2; Claims 3 to 5; or Claim 6 respectively, are in fact included in the claimed matter (Article 6 PCT).
Otherwise the claimed subject-matter is obvious in view of D2 to D5 (see under paragraph 6 above).

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : G01N 33/50, 33/68, C12N 9/12

A1

(11) International Publication Number: **WO 98/30902**

(43) International Publication Date: 16 July 1998 (16.07.98)

(21) International Application Number: PCT/GB98/00095

(22) International Filing Date: 13 January 1998 (13.01.98)

(30) Priority Data:

9700574.8	13 January 1997 (13.01.97)	GB
9713131.2	20 June 1997 (20.06.97)	GB

13 July 99

(71) Applicant *(for all designated States except US)*: CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED [GB/GB]; Cambridge House, 6–10 Cambridge Terrace, Regent's Park, London NW1 4JL (GB).

(72) Inventors; and

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(74) Agents: WALTON, Seán, M. et al.; Mewburn Ellis, York House, 23 Kingsway, London WC2B 6HP (GB).

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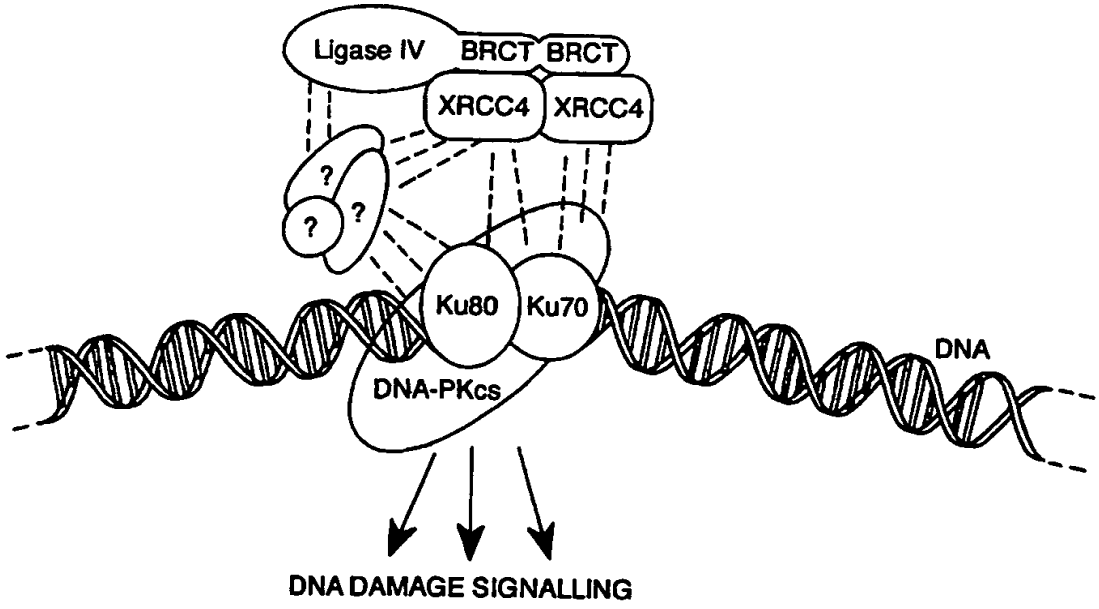
(54) Title: ASSAYS, AGENTS, THERAPY AND DIAGNOSIS RELATING TO MODULATION OF CELLULAR DNA REPAIR ACTIVITY



(57) Abstract

A yeast homologue of mammalian DNA ligase IV is provided and a role for DNA ligase IV established in the Ku–associated DNA repair pathway. Additionally interactions between DNA ligase IV and XRCC4, and interaction between XRCC4 and DNA–PKcs/Ku are established, providing for assays for agents which modulate such interactions and therefore cellular DNA repair activity. Such agents are useful in treatment of cancers, retroviral infections, immune system disorders and other conditions in which cellular DNA repair activity plays a role. Individuals with a predisposition to a disorder in which DNA repair plays a role may be diagnosed, by screening for the presence or absence of a defect in XRCC4 and/or DNA ligase IV activity.

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INTERNATIONAL SEARCH REPORT

Internat' Application No
PCT/GB 98/00095

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 G01N33/50 G01N33/68 C12N9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 17189 A (SALK INST FOR BIOLOGICAL STUDI) 4 August 1994 see claims 19-22 ---	1-28
X	POLTORATSKY, V.P. ET AL.: "human DNA activated protein kinase (DNA-PK) is homologous to phosphatidylinositol kinase." THE JOURNAL OF IMMUNOLOGY, 1995, pages 4529-44533, XP002065031 see the whole document --- -/--	7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
15 May 1998	19. 06. 1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hoekstra, S

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HIDAKA, H. ET AL.: "Methods in Enzymology volume 201; Protein phosphorylation part B analysis of protein phophorylation, protein kinas inhibitors and protein phosphatases; Ed. T. Hunter and B.M. Sefton; Chapter 27: "Properties and use of H-series compounds as protein kinase inhibitors" 1991 , ACADEMIC PRESS , SAN DIEGO XP002065037 see page 328 - page 339 ---	7
X	WEI, Y-F, ET AL.: "Molecular cloning and expression of human cDNAs encoding a novel DNA ligase IV and DNA ligase III, an enzyme active in DNA repair and recombination" MOLECULAR AND CLELLULAR BIOLOGY, vol. 15, no. 6, June 1995, pages 3206-3216, XP002065032 see the whole document ---	12
Y	GAKEN, JOOP A. ET AL: "Efficient retroviral infection of mammalian cells is blocked by inhibition of poly(ADP-ribose) polymerase activity" J. VIROL. (1996), 70(6), 3992-4000 CODEN: JOVIAM;ISSN: 0022-538X, XP002061469 see the whole document ---	1-28
Y	KACZMARSKI, WOJCIECH ET AL: "Lupus autoantigen Ku protein binds HIV-1 TAR RNA in vitro" BIOCHEM. BIOPHYS. RES. COMMUN. (1993), 196(2), 935-42 CODEN: BBRCA9;ISSN: 0006-291X, XP002061470 see the whole document ---	1-28
P,X	GRAWUNDER, U. ET AL.: "Activity of DNA ligase IV stimulated by complex formation with XRCC4 protein in mammalian cells" NATURE, vol. 388, 31 July 1997, pages 492-495, XP002065033 see the whole document ---	1-28
P,X	CRITCHLOW, S. E. ET AL.: "Mammalian double strand break repair protein XRCC4 interacts with DNA ligase IV." CURRENT BIOLOGY, vol. 7, no. 8, 1 August 1997, page 588-598 XP002065034 see the whole document --- -/--	1-28

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	TOMKINSON, A.E. ET AL.: "structure and function of mammalian DNA ligases" MUTAT. RES., vol. 407, no. 1, January 1998, pages 1-9, XP002065035 see the whole document	8-10
A	WO 96 30524 A (HUMAN GENOME SCIENCES INC ;WEI YING FEI (US); YU GUO LIANG (US); H) 3 October 1996	1-28
A	WO 95 10288 A (BAYLOR COLLEGE MEDICINE) 20 April 1995 see claim 1	1-28
A	SALLES B ET AL: "RAPID QUANTIFICATION OF DNA REPAIR SYNTHESIS IN CELL EXTRACTS" ANALYTICAL BIOCHEMISTRY, vol. 215, 1993, pages 304-306, XP002054958 see the whole document	1-28
A	HARTLEY, K. ET AL.: "DNA-dependent protein kinase catalytic subunit: A relative of phosphatidylinositol 3-kinase and the Ataxia telangiectasia gene product" CELL, vol. 82, 8 September 1995, pages 849-856, XP002065036 see abstract; figures 1-28	1-28

INTERNATIONAL SEARCH REPORT

Inte ional application No.
PCT/GB 98/00095

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: -
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATI N CONTINUED FROM PCT/ISA/ 210

Although claims 20, 23 and 26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the modulating compound.

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat[illegible]pplication No
PCT/GB 98/00095

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